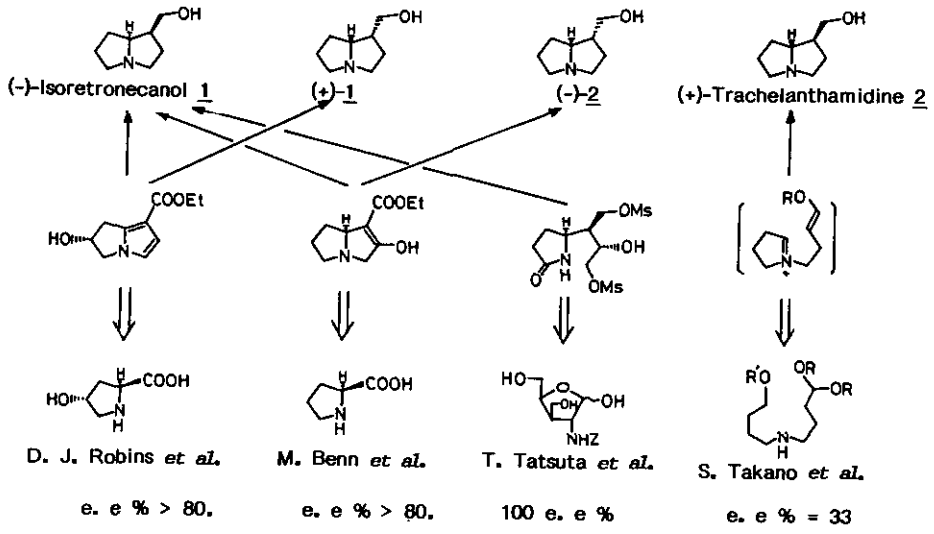
A NEW SYNTHESIS OF (-)-ISORETRONECANOL AND (-)-TRACHELANTHAMIDINE THROUGH ORTHOESTER CLAISEN REARRANGEMENT FOR ALLYLIC ALCOHOL FUNCTIONALITY TAGGED AT C(2) OF PYRROLIDINE AS A KEY STEP

Toshio Moriwake,* Shin-ichi Hamano, and Seiki Saito*
Department of Applied Chemistry, School of Engineering, Okayama University, Tsushima, Okayama, Japan 700

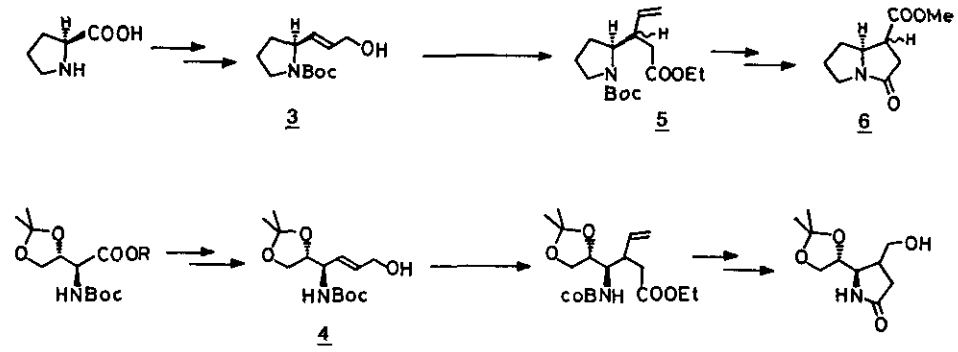
Abstract —— Orthoester Claisen rearrangement of (2S)-2-[1'(*E*)-3'-hydroxypropenyl]-pyrrolidine derived from (S)-proline gave (2S)-2-[1'-(ethoxycarbonylmethyl)-2'-propenyl]-N-(t-butoxycabonyl)-pyrrolidine which is ready for further elaboration directed to necine base skeleton. Title compounds have been synthesized using this key intermediate.

The pyrrolizidine alkaloids isolated from the pulse and the composite family are known to exhibit an incredible range of biological activity, including antitumor, hypotensive, and hepatotoxic actions, etc.[1] (-)-Isoretronecanol (1) and (-)-trachelanthamidine (2) are the simplest members of necine bases. Although many syntheses of 1 and 2 have been reported,[2] only a few reports for the synthesis of optically active 1 and 2 have appeared so far: D. J. Robins *et al.*,[3a] M. Benn *et al.*,[3b] K. Tatsuta *et al.*,[3c] S. Takano *et al.*,[3d] and Y. Nagao *et al.*[3e] have previously completed the total synthesis of both or either of these alkaloids employing starting materials and key intermediates indicated below, along with the outcomes of e.e.% achieved.

Recently we have established the general method for selective 1,2-reduction of γ-amino-α,β-unsaturated ester prepared from α-amino acid by means of BF_3·OEt_2 - DIBAL system[4] in which the added BF_3·OEt_2 plays an important role to coordinate electrophilically to the nitrogen atom, thereby to prevent the DIBAL from being trapped on the nitrogen atom. According to this procedure, we have prepared useful chiral allylic alcohol frameworks bearing amino functionality at γ-position such as 3 or 4, both of which can serve as a promising chiral building block for optically active necine bases family because an application of orthoester Claisen rearrangement to these may provide us with highly efficient route to 1-aza-bicyclo[3.3.0]- or right-hand portion of pyrrolizidine skeleton, respectively. In this communication, we will describe the total synthesis of 1 and 2 relying on such new method for constructing pyrrolizidine ring system using 3.



Scheme 1

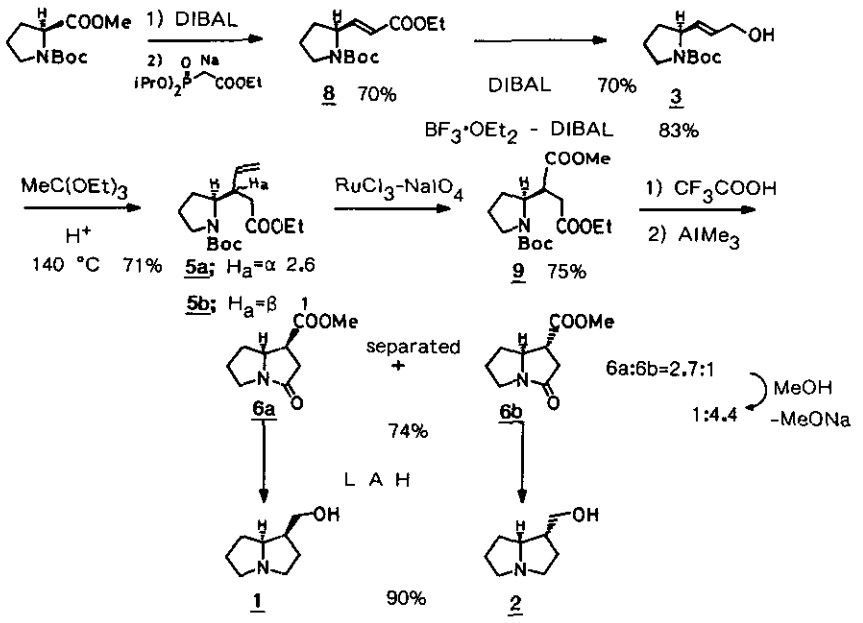


Scheme 2

In the event, N-boc-(S)-proline methyl ester was reduced with DIBAL [1 equiv./PhMe/-78°C], giving rise to N-boc-prolinal (7) in 74% crude yield,[5] which, without any purification, was subjectd to condensation with diisopropyl ethoxycarbonylmethylphosphonate [NaH/THF/0°C] to give 8 in 94% yield (>95% *E*) after silica gel purification: $[\alpha]_D^{22}$ -75.3° (c 1.74, $CHCl_3$). When the resulting γ-amino-α,β-unsaturated ester (8) was allowed to react with DIBAL [2 equiv./PhMe/-78°C], 4 was furnished in 71% yield accompanied by inevitable formation of 1,4-reduction product which made a purification of 3 very difficult. However, when 8 was reduced with DIBAL [2 equiv.] after being exposed to BF_3·OEt_2 [1 equiv.] in CH_2Cl_2 at -78°C for 0.5 h, 4-amino-allylic alcohol (3) was obtained in higher yield (83%) after column chromatography, a negligible amount of 1,4-reduction product being detected: $[\alpha]_D^{20}$ -30.3° (c 2.88, $CHCl_3$); ir (film) 3380 (OH), 1675 (boc); ^{1}H-nmr ($CDCl_3$) δ 1.43 (s, 9H), 1.67-12.18 (m, 4H), 3.05-3.60 (m, 3H), 4.01-4.72 (m, 3H), 5.64 (m, 2H); ^{13}C-nmr ($CDCl_3$) δ 23.20 (t),

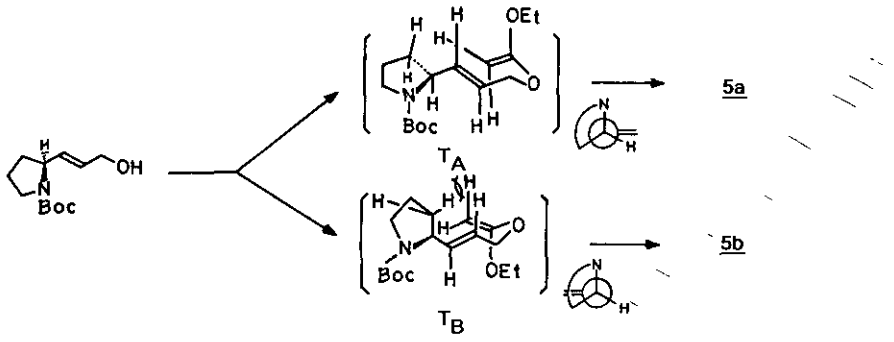
128.51 (q), 31.92 (t), 46.40 (t), 58.24 (d), 62.48 (t), 79.20 (s), 129.3 (d), 131.4 (d), 154.7 (s).

The next key step which leads to a proper arrangement of requisite carbon framework have been effected by orthoester Claisen rearrangement of 3 [$CH_3C(OEt)_3$/EtCOOH/140°C][6] to afford (2S)-2-[1'-3'-ethoxycarbonylmethyl)-2'-propenyl]]-N-boc-pyrrolidine (5)[7] in 71% yield, new chiral carbon being generated simultaneously. Diastereofacial selectivity of this orthoester Claisen rearrangement turned out to be about 2.6 : 1 (5a:5b) estimated on the basis of ^{13}C-nmr spectra (25.05 MHz). The mixture of diastereoisomers 5 was subjected to ruthenium-catalyzed oxidation[8] [$RuCl_3 \cdot H_2O$, 0.05 equiv./$NaIO_4$, 10 equiv./CCl_4:MeCN:H_2O=1:1:1.5/room temperature] to afford carboxylic acid, which, without purification, was treated with CH_2N_2 [AcOEt/0°C] to give 7 in 75% yield after silica gel chromatography. A generation of free amino group and ensuing intramolecular amidation by means of $AlMe_3$[9] gave rise to (5S)-4-methoxycarbonyl-1-azabicyclo[3.3.0]octan-2-one (6) in 74% yield. The diastereoisomer ratio of 9 turned out again to be approximately 2.6 : 1 (6a:6b) as verified on the basis of capillary gas chromatographic analysis. The two diastereoisomer have been separated carefully using silica gel column chromatography and both isomers, 6a[10] $[\alpha]_D^{22}$ -135.5° (c 1.4, $CHCl_3$) and 6b[11] $[\alpha]_D^{21}$ -80.4° (c 1.5, $CHCl_3$), were identified on careful comparison with ^{1}H- and ^{13}C- nmr spectral data of the authentic one.[12] We expected that the major *endo*-stereoisomer (6a) would be readily epimerized to the thermodynamically more stable *exo*-stereoisomer (6b). Thus, the amide ester 6 was actually transformed into a 1 : 4.4 mixture of 6a and 6b (capillary gas chromatographic analysis) in 76% yield by



Scheme 3

treatment with excess sodium methoxide in MeOH at ambient temperature for 24 h. A simultaneous reduction of both ester and amide groups of 6a and 6b by LAH in THF[12] led to (-)-isoretronecanol (1); $[\alpha]_D^{23}$ -76.4° (c 1.3, EtOH) [lit. $[\alpha]_D^{27}$ -78.2° (c 2.8, EtOH)][13], and (-)-trachelanthamidine (2); $[\alpha]_D^{23}$ -13.4° (c 0.5, EtOH) [lit. $[\alpha]_D$ -13.8° (c 1.28, EtOH)][14], respectively, in 90% yield.



Scheme 4

It is generally known that the Claisen rearrangement proceeds usually through a chair-like six-membered cyclic transition state.[15] Under such situation, two representative transition states such as T_A and T_B could be considered. The above-mentioned results indicate that T_A is more favorable than T_B or, in other wards, the *re*-face of allylic olefin may be the least hindered site to give 5a as a major isomer. An appropriate model suggests that such conformations as T_A or T_B would be realized if the C-N bond orients orthogonal to the C=C plane so as to maximize an overlapping between σ^*(C-N) and π(C=C) orbitals.[16] We have also attempted Ireland rearrangement for the acetate of 3 [LDA/Me_3SiCl/THF-HMPA] in the hope of improving the observed diastereoselectivity not to be fruitful.[17] Application of the present strategy to the total synthesis of heliotridine or retronecine employing 4 is currently a major concern in our laboratory.

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7) 5: ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.24 (t, J=7.6 Hz, 3H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$), 1.60-1.91 (bm, 4H, CH_2CH_2), 2.20-2.33 (m, 2H, CH_2COOEt), 2.76-3.60 (m, 3H, NCH_2, CHC=C), 3.70-4.02 (b, 1H, NCH), 4.12 (q, J=7.6 MHz, 2H, OCH_2), 4.93-5.16 (m, 2H, $C=CH_2$), 5.44-5.86 (m, 1H, CH=C); The ^{13}C-nmr ($CDCl_3$, 25.05 MHz) spectrum showed a mixture of two isomer; major isomer (5a) δ 14.28 (q), 23.64 (t), 28.46 (q), 31.97 (t), 36.94 (t), 44.17 (d), 47.23 (d), 60.19 (d,t), 79.39 (s), 116.5 (t), 138.1 (d), 154.9 (s), 172.5 (s); minor isomer (5b) δ 14.28 (q), 23.64 (t), 27.68 (t), 31.97 (t), 36.94 (t), 43.72 (d), 46.69 (d), 60.19 (d,t), 79.39 (s), 117.3 (t), 136.8 (d), 154.9 (s), 172.5 (s).

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10) 6a: ^{1}H-nmr ($CDCl_3$, 500 MHz) δ 1.81-1.88 (m, 1H, C(7)H), 1.93-2.12 (m, 3H, C(6)H2, C(7)H), 2.78-2.82 (m, 2H, C(2)H2), 3.04 (ddd, J=13, 11, 3.1 Hz, 1H, C(5)H), 3.39 (dd, J=18, 5.4 Hz, d, J=5.4 Hz, 1H, C(1)H), 3.58 (m, 1H, C(5)H), 3.70 (s, 3H, CH_3), 4.09 (dd, J=14, 4.6 Hz, dd, J=5.4, 1.8 Hz, 1H, C(8)H); ^{13}C-nmr ($CDCl_3$, 126 MHz) δ 26.01 (t), 2742 (t), 36.05 (t), 39.56 (d), 41.71 (t), 51.92 (q), 62.68 (d), 172.23 (s), 174.04 (s).

11) 6b: ^{1}H-nmr ($CDCl_3$, 500 MHz) δ 1.94-2.09 (m, 2H, C(6)H2), 2.09-2.20 (m, 2H, C(7)H2), 2.69 (ddd, J= 15, 8.2, 1.9 Hz, 1H, C(2)H_β), 2.94-3.11 (m, 3H, C(1,5)2H, C(2)H_α), 3.56 (dd, J=18, 8.5 Hz, 1H, C(5)H), 3.72 (s, 3H, OCH_3), 4.04 (q, J=6.6 Hz, 1H, C(8)H); ^{13}C-nmr ($CDCl_3$, 126 MHz) δ 26.72 (t), 31.66 (t), 38.51 (t), 41.24 (t), 45.86 (d), 52.31 (q), 63.77 (d), 172.05 (s), 172.48 (s).

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